Clinical Neurophysiology 126 (2015) 558–564

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Significance of multiple neurophysiological measures in patients with chronic disorders of consciousness

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ARTICLE INFO

Article history:
Accepted 2 July 2014
Available online 11 July 2014

Keywords:
Disorders of consciousness
Evoked potentials
EEG
Relative power
Sleep score
Cluster analysis

HIGHLIGHTS

- Preservation of spatially distributed EEG alpha characterises patients in an MCS.
- The maintenance of variable sleep patterns is a strong indicator of the severity of the disorder of consciousness (DOC).
- The combination of EP and EEG patterns helps to classify chronic DOCs.

ABSTRACT

Objective: The aim of this study was to verify the value of multiple neurophysiological tests in classifying disorders of consciousness (DOCs) in patients in a chronic vegetative or minimal consciousness state categorised on the basis of the Coma Recovery Scale (CRS).
Methods: The study included 142 patients, all of whom underwent long (18 h) EEG-polygraphic recordings including one night. The EEG was scored using the Synek scale and sleep patterns using an arbitrary scale. Absolute total power and relative EEG power were evaluated in different frequency bands. Multimodal evoked potentials (EPs), including auditory event-related potentials, were also evaluated and scored.
Results: The most information came from the combined multimodal EPs and sleep EEG scores. A two-step cluster analysis based on the collected information allowed a satisfactory evaluation of DOC severity. Spectral EEG properties seemed to be significantly related to DOC classes and CRS scores, but did not seem to make any significant additional contribution to DOC classification.
Conclusions: Multiple electrophysiological evaluations based on EEG, sleep polygraphic recordings and multimodal EPs are helpful in assessing DOC severity and residual functioning in patients with chronic DOCs.
Significance: Simple electrophysiological measures that can be easily applied at patients' bedsides can significantly contribute to the recognition of DOC severity in chronic patients surviving a severe brain injury.

1. Introduction

EEG recordings and evoked potentials (EPs) are currently used to evaluate patients with disorders of consciousness (DOCs), and many published data indicate their importance when assessing the degree of brain damage and formulating the prognosis of patients in the early stages of DOCs (Guérit et al., 2009; Boccagni et al., 2011; Koenig and Kaplan, 2013). In addition to the simplest conventional measures based on the qualitative visual evaluation of EEG traces or the use of *ad hoc* scales (Synek, 1988), a number of analytical algorithms aimed at extracting quantitative parameters or detecting qualitative changes in cortico-cortical or

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http://dx.doi.org/10.1016/j.clinph.2014.07.004
1388-2457/

cortico-thalamic coupling have been applied to resting EEG signals in an attempt to enhance their ability to classify the severity of brain damage or assess its prognosis (see for example Gosseries et al., 2011; Lehembre et al., 2012; Fingelkurts et al., 2012, 2013a,b; Holler et al., 2014). It has also been shown that brief latency EPs and cognitive responses to simple or complex stimuli (Kaplan, 2006; Estraneo et al., 2013) can be used to detect and measure residual brain function.

Most published studies have involved patients observed shortly after the brain insult, but there is limited information concerning the effectiveness of neurophysiological measures in classifying chronic DOCs in subjects observed after several months or years. Chronic patients are often included in case series, but very few studies have specifically evaluated these particular neurological conditions (De Salvo et al., 2012; Fischer et al., 2010; Fingelkurts et al., 2013a) and, although they often refer to specific neurophysiological tests, the tests themselves have not been compared with each other.

This paper describes the results obtained by evaluating 142 patients with chronic DOCs using various neurophysiological measures (visual EEG evaluation, sleep EEG patterns during long-lasting recordings, estimated EEG spectral composition, and the evaluation of multimodal EPs including auditory event-related potentials), all of which have been extensively used to assess virtually all of our patients classified as being in a vegetative state (VS) or minimal consciousness state (MCS) on the basis of clinical scales (Giacino et al., 1997, 2004). The aim of the study was to evaluate the ability of these measures to classify DOC severity and assess residual functioning.

2. Methods

2.1. Patients

The study involved all of the adult patients admitted consecutively to the C. Besta Foundation Neurological Institute in order to be evaluated at the start-up Coma Research Centre between February 2011 and 2013. The neurophysiological tests were performed during the second and third day after admission.

The 142 patients were aged 50.9 ± 14.1 years and observed 38.8 ± 34.6 months after an acute brain insult. They were assessed using the Italian version of the Coma Recovery Scale-Revised (CRS-R) (Lombardi et al., 2007), and the definitions of VS and MCS were based on the CRS-R items designed for this purpose according to the Aspen criteria (Seel et al., 2010). The patients were further grouped on the basis of the etiology of the brain insult: anoxic (ABI), traumatic (TBI), or vascular (VBI).

Eighty-five patients (29 women) were classified as being in a VS (59.9%; age 51.8 ± 13.8 years; time after insult 33.3 ± 35.6 months; >12 months in 78.8% of cases) and 57 (23 women) as being in an MCS (age 49.6 ± 14.5 years; time after insult 47.2 ± 44.4 months; >12 months in 85.9% of cases). The differences in age, gender and time after the acute brain insult were not statistically significant.

The DOCs were due to an ABI in 53 patients (83.3% in a VS), a TBI in 40 (53.8% in a VS), and a VBI in 49 (38.8% in a VS). The study was approved by the Ethics Committee of the C. Besta Foundation Neurological Institute in Milan, Italy, and written informed consent was obtained from the patients' legal representatives.

2.2. Neurophysiological measures

The patients were not sedated during any of the neurophysiological evaluations, and all of the tests were carried out at the patients' bedsides. All of the measures and scores were independently determined by two expert neurophysiologists who were blinded to the final CRS scores and DOC classification at the time of the evaluation.

2.3. EEG recordings

The EEG and polygraphy (EOG, ECG, sub-mental EMG) recordings were made by means of Ag/AgCl surface electrodes (impedance <5 kΩ) and acquired at a sampling rate of 256 Hz using a computerised system (Micromed SpA, Mogliano Veneto, Treviso, Italy). The raw EEG signals were recorded against a common reference electrode in order to allow off-line data reformatting. All of the polygraphic recordings were made using a 19 EEG electrode array placed according to the 10–20 International System; they were started at 2 p.m. and ended at 9 a.m. on the following day, and included, EOG, EMG from the sub-mental muscle, a bipolar precordial ECG derivation and an impedance thoracic pneumogram.

The EEG pattern was visually evaluated and scored using the Synek scale (Synek, 1988) with five grades (1 = reactive alpha–theta; 2 = predominant theta; 3 = predominant delta/spindles; 4 = burst suppression / alpha coma / theta coma / low voltage delta; and 5 = electrocerebral silence).

The spectral EEG analysis was based on 5-min, artefact-free EEG epochs starting from 10 s after the end of the response to arousal stimuli, when the EMG artefacts had virtually disappeared and the patients had closed their eyes, but in the absence of any change in the EEG or polygraphic parameters suggesting "sleep" behaviour. The EEG epochs with continuous epileptiform activities (e.g. periodic lateralised epileptiform discharges) were excluded.

The EEG epochs were filtered (1–70 Hz, 12 db/octave) followed by a 50 Hz notch filter to suppress the noise of the electrical power line. The selected EEG epochs were reformatted against the linked ear-lobe reference, and analysed using the fast Fourier transform (FFT). Three minutes of EEG activity were analysed by dividing it into 90 non-overlapping 2-s segments. Absolute total power (TPW) and relative power (RP) were evaluated in the delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz) and beta bands (13–30 Hz), and averaged within each EEG channel. The gamma band was excluded because of possible contamination with high-frequency residual muscle activity. The mean RP of each band of interest was averaged over the whole set of electrodes; moreover, the electrodes were grouped into four regions of interest (ROIs): fronto-central (FC: Fp1, Fp2, F3, F4, C3, C4), parieto-occipital (PO: P3, P4, O1, O2), temporal (T: F8, T4, T6; F7, T5, T3), and midline (Mid: Fz, Cz, Pz).

2.4. Sleep

Sleep was evaluated by means of the visual inspection of epochs characterised by regular breathing, a steady heart rate, and the disappearance of blink and EMG artefacts, and was scored using an arbitrary scale: 0 = undetectable EEG changes; 1 = epochs of signal attenuation appearing as a predominant pattern; 2 = brief epochs of signal attenuation alternating with sequences of slow activity, often including epileptiform transients; 3 = epochs of delta sleep repeatedly occurring during the same recording; and 4 = long EEG epochs with a multiple pattern conceivably equivalent to different stages of slow-sleep, mainly occurring in the late evening and during the night.

2.5. Evoked potentials

Multimodal EPs and event-related potentials (ERPs) were recorded using the Galileo Mizar System (EBNeuro, Florence, Italy) and standard laboratory procedures, including multiple trials for each test.